REVIEW ARTICLE

Soluble syndecans: biomarkers for diseases and therapeutic options

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Syndecans are important mediators of signalling by transmitting external stimuli into the cells. This role in signal transduction has been attributed mainly to the membrane-bound syndecans. In the last years, however, the soluble ectodomain of syndecans generated by shedding has come into the focus of research as this process has been show to modulate the syndecan-dependent signalling pathways, as well as other pathways. This review summarizes the current knowledge about the induction of syndecan shedding and the different pathways modulated by shed syndecan proteins. This review summarizes the known and putative sheddases for each syndecan and describes the exemplary conditions of sheddase activity for some syndecans. This review summarizes the proposed use of shed syndecans as biomarkers for various diseases, as the shedding process of syndecans depends crucially on tissue- and disease-specific activation of the sheddases. Furthermore, the potential use of soluble syndecans as a therapeutic option is discussed, on the basis of the current literature.

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Abbreviations

ADAMs, a disintegrin and metalloproteinase; ECM, extracellular matrix; FAK, focal adhesion kinase; GAG, glycosamino-glycan; HS, heparan sulfate; Sdc, syndecan; TACE, TNF-α-converting enzyme, ADAM-17; VEGFR2, VEGF receptor 2

Syndecan structure

Syndecans belong to the family of type I transmembrane heparan sulfate proteoglycans, which consist of four members in vertebrates (Sdc1, Sdc2, Sdc3 and Sdc4). The core protein of these proteoglycans is composed of an extracellular, transmembrane and intracellular domain (Figure 1). Sdc1, Sdc2 and Sdc4 are translated with a signal peptide, which is cleaved during the processing of the protein (Figure 1). All syndecans span the plasma membrane via a 24–25 amino acid long hydrophobic transmembrane domain. The transmembrane domain includes a GXXXG motif, which allows for a strong, SDS-resistant homodimerization of syndecans (Choi et al., 2005). The transmembrane and cytoplasmic domains share approximately 60–70% amino acid sequence identity between all family members (David, 1993).

The membrane proximal region C1 is highly conserved among all syndecans (90%) and also among different species, as well as the C-terminal C2 region (100% conservation between syndecans). These two domains flank a variable region V1, which differs for each syndecan and exhibits only 15% similarity between all syndecans (Figure 1). However, Sdc1 and Sdc3 have a higher similarity in this variable region, as well as Sdc2 and Sdc4. This finding gave rise to the assumption that these members of the syndecan family are more closely related to each other than to the others (Carey, 1997).

The ectodomains of syndecans share only weak homology between all four members (Figure 1). The putative glycosaminoglycan (GAG) attachment sites have similar consensus sequences. Two attachment sites have the consensus sequence SGXG, and three others have the consensus sequence (E/D) GSG (E/D). The existence of GAG binding sites either at both ends of the ectodomain (Sdc1 and Sdc3) or only at the distal part (Sdc2 and Sdc4) of the ectodomain is another indicator for the subclassification of syndecans (Elenius and Jalkanen, 1994). Syndecans have predominantly heparan sulfate-GAG (HS-GAG) chains attached to the extracellular domain and in the case of Sdc1 and Sdc3, additionally chondroitin sulfate GAG chains (Deepa et al., 2004).

The extracellular domain of all syndecans contains a proteinase-sensitive dibasic lysine-arginine-site (KR in Sdc2 and Sdc4) or arginine-lysine-site (RK in Sdc1, Sdc2 and Sdc3) adjacent to the transmembrane domain. This site was proposed to be a cleavage site for plasmin and thrombin. In 1989, the shedding of Sdc1 at this site was described by (Saunders et al., 1989). Also, thrombin cleaved the Sdc4 at the Lys^{114}–Arg^{115} link (Schmidt et al., 2005). There are currently no data on the plasmin-dependent and thrombin-dependent shedding of Sdc2 and Sdc3, but it is likely that both can be shed at the respective sites. Furthermore, as discussed later in this review, several different shedding sites are located in the extracellular part of the protein.

Figure 1

Sequence alignment of all syndecan family members. The alignment indicates the different regions for each syndecan, including signal peptide (green), extracellular domain (yellow), transmembrane domain (blue) and intracellular domain (red). Furthermore, the homodimerization domain within the transmembrane region is marked in grey. Black bars indicate the C1, C2 and V region within the intracellular domain (Uniprot UniProt website at http://www.uniprot.org/).

Syndecan expression

Syndecans are involved in growth control, cell spreading, cellular recognition, cellular adhesion and signal transduction (Couchman, 2010; Choi *et al*., 2011). Each syndecan has a tissue-specific and developmentally regulated pattern of expression (Kim *et al.,* 1994). For example, during murine development, Sdc1 is expressed first in the ectoderm and later on in mesodermal cells (Sutherland *et al*., 1991). In mature tissue, epithelial cells permanently express Sdc1 (Kim *et al*., 1994). The expression of Sdc3 is found during skeletal and neural development, where it is supposed to complement the function of Sdc1 (Bernfield *et al*., 1993; Kim *et al*., 1994). Sdc2 and Sdc4 are also expressed during mouse embryogenesis, specifically during endochondral ossification (David, 1993; Bertrand *et al*., 2013). In contrast to the other syndecans, Sdc4 is expressed ubiquitously (Kim *et al*., 1994).

As mentioned before, syndecans are mediators of various cellular functions. One explanation for how syndecans can fulfil all these functions might be the differential regulation of their expression during development and disease. For example, Sdc4 exhibits a major function in regulating cell matrix remodelling under inflammatory conditions, such as wound healing, fracture healing and osteoarthritis (Echtermeyer *et al*., 2001; Echtermeyer *et al*., 2009; Bertrand *et al*., 2013). To exert this function, the expression of Sdc4 is regulated in an NFκB-dependent manner, thereby explaining the increased expression under inflammatory conditions (Zhang *et al*., 1999; Wang *et al*., 2014). Apart from the specific regulation of expression, syndecans are able to initiate downstream signalling cascades via the C1 region, located just beneath the membrane, which is thought to interact with the cell cytoskeleton and cellular Src kinase proteins (Kinnunen *et al*., 1998). Also, the C2 region, which contains a PDZ1 or PDZ2 domain, binds adaptor proteins, and the interaction mediates vesicular trafficking and exosome biogenesis (Gao *et al*., 2000; Baietti *et al*., 2012). The V region is thought to determine the role of syndecans in downstream signalling processes (Afratis *et al*., 2017).

Beside this direct syndecan-dependent activation of signalling cascades, syndecans interact via their HS-GAG chains with a variety of ligands such as growth factors, cytokines, proteinases, adhesion receptors, extracellular matrix (ECM) components and morphogens (Pap and Bertrand, 2013). These HS-protein interactions are evolutionarily conserved and strongly HS-sequence and especially sequence modification specific. Various enzymes are needed for the maturation of HS-GAG chains, including multiple glycosyltransferases, sulfotransferases and an epimerase. It is known that many different cell types produce HS chains with several post-translational modifications, which determine the activation of downstream signalling cascades (Gesteira *et al*., 2011; Shah *et al*., 2011; Mortier *et al*., 2012). This massive influence of HS-GAG chain modifications on signal transduction is explained by the fact that these modifications modulate the binding capacity of morphogens and chemokines, as, for example, the 6-O-sulfation of HS-GAG chains seems to be necessary for activation of FGF and Wnt signalling (Dhoot *et al*., 2001; Wang *et al*., 2004)

Interestingly, mutations in most of these HS-GAG modifying enzymes are associated with different diseases, including various malfunctions during skeletal development (Koziel

et al., 2004; Kluppel *et al*., 2005; Otsuki *et al*., 2008; Otsuki *et al*., 2010; Otsuki *et al*., 2017) and neuronal network formation (Rhiner and Hengartner, 2006).

Upon binding of different morphogens to the GAG chains, syndecans on the one hand interact with the respective receptor at the cell surface. On the other hand, it has been shown that syndecans can be shed from the cell surface to build morphogen gradients throughout the ECM, making the shedding a relevant process in syndecan-dependent signalling pathways.

Shedding

It has been known for many years that syndecans link the cytoskeleton to the ECM (Rapraeger *et al*., 1986). One of the first publications about syndecan shedding described this process as an attempt of cells to release themselves from this interaction with the ECM by a proteolytic cleavage (Jalkanen *et al*., 1987). Today, it is known that under physiological conditions, the ectodomains of syndecans are constitutively shed to a small degree. This shedding rate can be substantially increased in response to external stimuli (Kim *et al*., 1994; Manon-Jensen *et al*., 2010). This review gives a broad overview about different pathways and mechanisms activated and or modulated by the shed syndecans. There are certainly more sheddases and downstream activated pathways, which are not mentioned in this section, which are detailed in shedding specific reviews (Manon-Jensen *et al*., 2010; Nam and Park, 2012).

Different sheddases are able to cleave syndecans on the extracellular side, releasing a soluble syndecan consisting of the extracellular domain and the attached GAG chains (Brule *et al*., 2006; Pruessmeyer *et al*., 2010). These soluble syndecans may function as paracrine or autocrine effectors, or function as decoy receptors by competing for the same ligands as their cell bound counterparts (Kainulainen *et al*., 1998) (Figure 2A and B). These cleaved fragments contain intact HS-GAG chains that retain biological activity similar to that of their parent molecule. These fragments still have the ability to down-regulate signal transduction by competing with the membrane-bound syndecans for extracellular ligand binding and sequestering the HS binding factors in ECM (Hayashida *et al*., 2008) (Figure 2A).

Soluble ectodomains of syndecans, however, do not only function as competitive inhibitors but can also work as agonists. For example, the ectodomain of Sdc1 binds to FGF-2 more efficiently than the cell surface bound Sdc1 and inhibits its mitogenicity (Su *et al*., 2007). Upon degradation of the GAG chains attached to the soluble Sdc1 ectodomain by heparanase present in the wound fluids, FGF-2 is activated to enhance wound repair (Kato *et al*., 1998; Yang *et al*., 2002; Mahtouk *et al*., 2007). Hence, syndecans have diverse functions both as membrane bound and soluble forms. Therefore, soluble syndecans can also help form morphogen gradients across tissues that influence cell behaviour, for example, migration in tissue repair (Li *et al*., 2002; Manon-Jensen *et al*., 2010) (Figure 2B).

Furthermore, heparanase, an endo-β-D-glucuronidase, plays a role in the shedding of syndecans. This fact is counterintuitive, as heparanase is known only to cleave the HS-
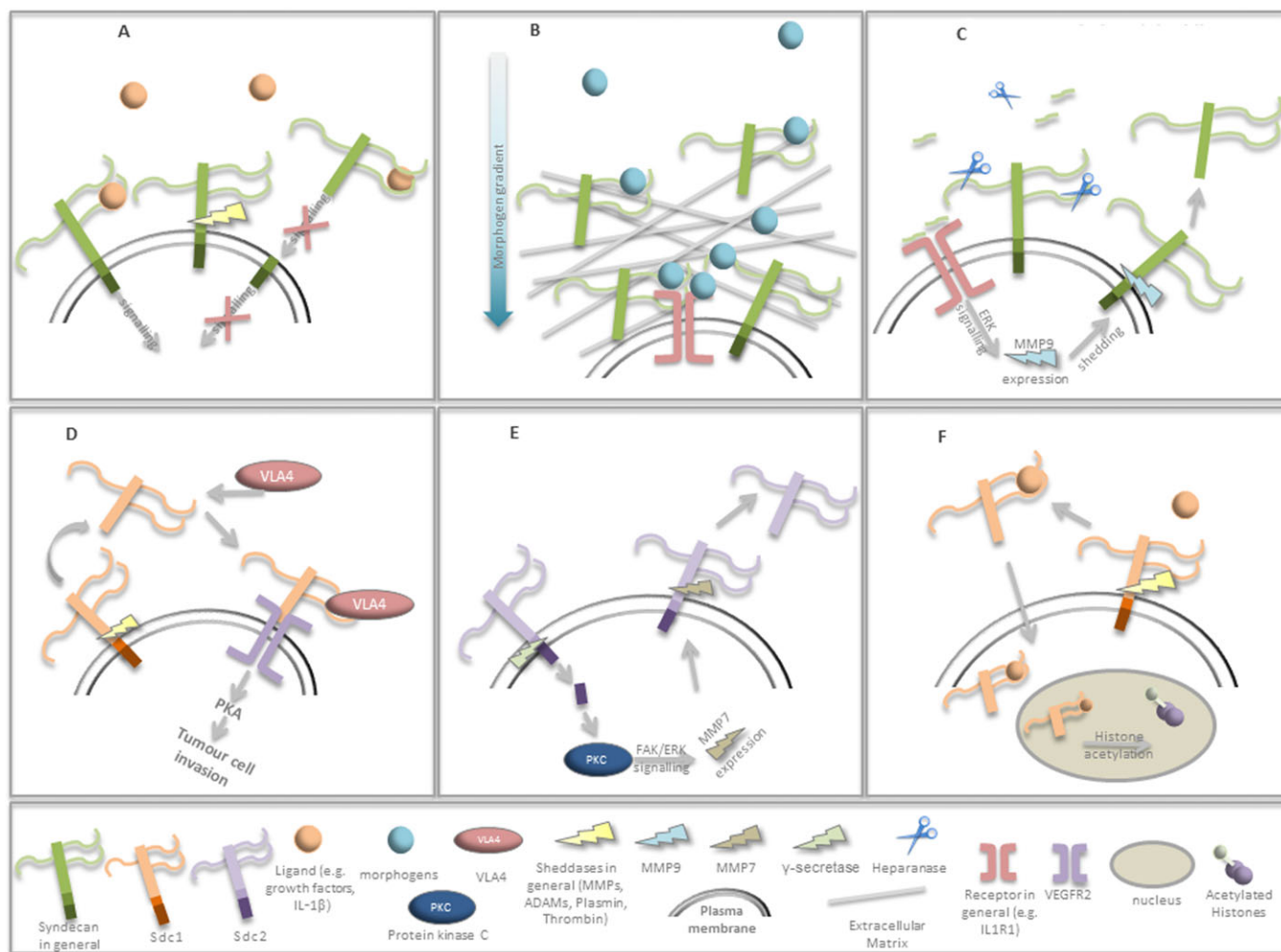
Figure 2

Schematic representation of different effects of shed syndecans on signalling cascades. The diagram depicts the various signalling influences of soluble syndecans on downstream signalling cascades that are discussed in the text. (A) Decoy receptor; (B) morphogen gradient; (C) heparanase-induced shedding; (D) receptor activation by shed Sdc1; (E) C-terminal fragment signalling; (F) shed syndecan in the nucleus.

GAG chains of proteoglycans but not the core protein of syndecans (Pikas *et al.*, 1998). The enhanced shedding of syndecans activated by heparanase is mediated indirectly, via the up-regulation of MMP9 and induction of ERK signalling (Purushothaman *et al.*, 2008) (Figure 2C). It has been shown that the 2-O-sulfated HS-GAG chains of Sdc1 inhibit neutrophil-dependent cathelicidin secretion, thereby promoting *Staphylococcus aureus* infection (Hayashida *et al.*, 2015). These data indicate that the main effect of heparanase on syndecan shedding is the activation of inflammatory signalling cascades, inducing the production of sheddases.

Soluble syndecans can also help form morphogen gradients due to the factors attached to the HS-GAG chains. Furthermore, the cleaved HS-GAG chains themselves can induce cellular responses. Interestingly, shedding of Sdc1 exposes a cryptic domain on the soluble core protein that contains binding sites for VLA4 and VEGF receptor 2 (VEGFR2). The shed Sdc1 activates VEGFR2 and stimulates thereby tumour cell invasion (Jung *et al.*, 2016) (Figure 2D).

During the shedding of the external part of syndecan, also, a C-terminal membrane-bound fragment is generated (Fitzgerald *et al.*, 2000). These C-terminal syndecan fragments are further cleaved at the transmembrane region by presenilin-dependent γ secretase upon ectodomain shedding (Schulz *et al.*, 2003). The C-terminal Sdc2 fragment up-regulates MMP7 expression via the protein kinase Cγ-mediated focal adhesion kinase (FAK)/ERK signalling pathway in colon cancer, thereby up-regulating its own shedding (Jang *et al.*, 2017) (Figure 2E).

Interestingly, the shed syndecan fragment can be taken up by cells, as it has been shown that shed Sdc1 translocated to the nucleus of cells delivering growth factors and inhibiting histone acetylation (Stewart *et al.*, 2015) (Figure 2F).

Syndecan ectodomain shedding is mediated by various MMPs, such as MMP2, MMP7 and MMP9 (Schlondorff and Blobel, 1999; Arribas and Borroto, 2002). Furthermore, plasmin and thrombin have been shown to function as sheddases for syndecans (Schmidt *et al.*, 2005; Wang *et al.*, 2005).

Shedding of Sdc1 and Sdc4 is accelerated by activation of thrombin and the EGF. This shows that proteases and growth factors, which are active during wound repair, can accelerate syndecan shedding from cell surfaces (Subramanian *et al.*, 1997). Interestingly, MMPs cleave syndecans at the juxtamembrane site in a process that is usually accelerated during diseased conditions (Manon-Jensen *et al.*, 2010). The disintegrin and metalloproteinases (ADAMs), however, cleave Sdc4 near the N-terminal tip of the first HS-GAG chain attachment site (Gao *et al.*, 2004; Rodriguez-Manzaneque *et al.*, 2009) (Figure 3).

Sdc1 contains the general consensus motif for cleavage by MMP7, MMP9 and MMP14, and *in vitro* and *in vivo* evidence of shedding has been published (Li *et al.*, 2002; Endo *et al.*, 2003). Chen *et al.* (2009) showed that epithelial injury induced Sdc1 shedding from the epithelium of wild-type mice but not from the epithelium of MMP7 knockout mice, indicating an essential role for MMP7 in the shedding process. A very recent study showed that MMP14 sheds Sdc1 during liver fibrosis, where the soluble Sdc1 interferes with TGF-β1 signalling and thereby up-regulates its own sheddase (Regos *et al.*, 2018). The gelatinases MMP2 and MMP9 have been shown to shed Sdc1, Sdc2 and Sdc4 (Brule *et al.*, 2006; Fears *et al.*, 2006). Controversial data have been published on the involvement of TNF-α-converting enzyme, ADAM-17 (TACE), in the shedding of syndecans. Fitzgerald found that ectodomain shedding of Sdc1 and Sdc4 is TACE independent (Fitzgerald *et al.,* 2000). Later, it was found that the shedding of Sdc1 and Sdc4 is stimulated by the recombinant TACE catalytic domain (Pruessmeyer *et al.*, 2010). Sdc3 shedding has been reported in Schwann cells obtained from the sciatic nerves of 2- to 4-day-old rats (Asundi *et al.*, 2003). As the shedding process was reduced in cells treated with an MMP inhibitor, the involvement of MMPs in mediating Sdc3 shedding is very likely (Asundi *et al.*, 2003) (Figure 3).

These results indicate that syndecans can be the substrate of more than one sheddase, suggesting that different sheddases act in a tissue-specific manner. The different functions of the various shed fragments and their attached factors are still not fully understood, but it has become clear that shed syndecans influence signalling cascades in several different ways. As shedding of syndecans is specifically regulated under disease conditions, soluble syndecan ectodomains are used as biomarker for various diseases.

Shed syndecans as biomarkers for different diseases

Syndecan shedding has been shown to regulate many pathophysiological processes, such as inflammation, tissue repair and cancer cell proliferation (Maeda *et al.*, 2004). Tissue injury is accompanied by cellular stress, accumulation of leukocyte-derived proteases (thrombin, plasmin, elastase, etc.) and release of growth factors, each of which may accelerate syndecan shedding (Subramanian *et al.*, 1997). For this reason, shed syndecan ectodomains are found in inflammatory fluids, where they are thought to maintain proteolytic and growth factor balance (Subramanian *et al.*, 1997), as well as mediating inflammation (Fitzgerald *et al.*, 2000). A detailed list of the different diseases for which shed Sdc1, Sdc2, Sdc3 and Sdc4 have been proposed as biomarkers is given in Table 1. We provide here some typical studies on shed syndecans as biomarkers for various diseases.

Most publications on soluble syndecans as biomarkers focus on soluble Sdc1. For example, Sdc1 ectodomains are elevated in blood of patients with sepsis (Nelson *et al.*, 2008; Steppan *et al.*, 2011), ischaemia–reperfusion injury (Rehm *et al.*, 2007), graft-versus-host disease (Seidel *et al.*, 2003) and various cancers (Joensuu *et al.*, 2002; Yang *et al.*, 2002). Furthermore, studies in mice have shown that the
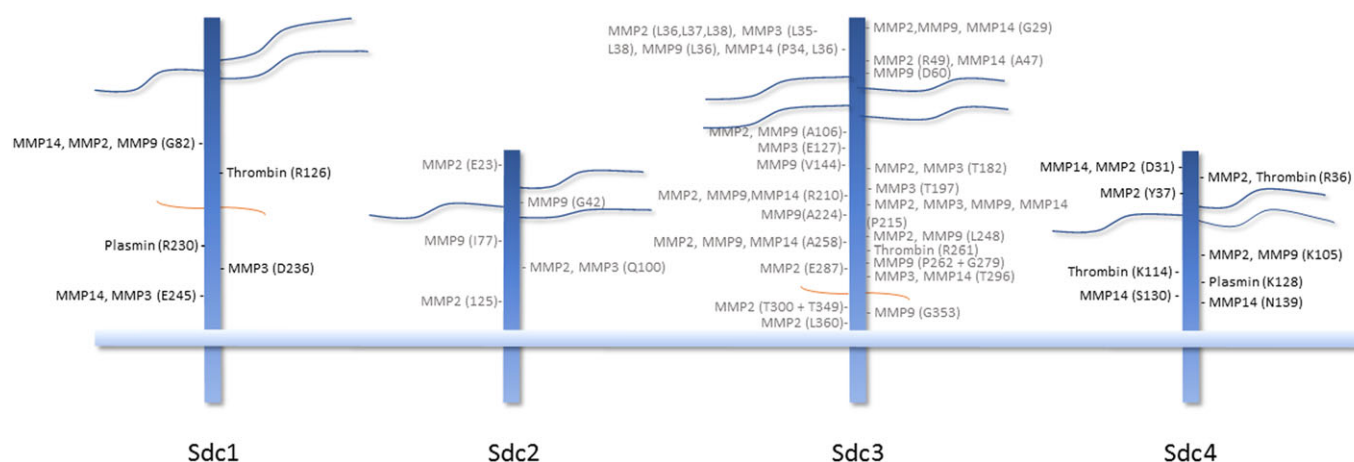
Figure 3

Overview of the proteinase cleavage sites on the syndecan ectodomains. The validated shedding sites for Sdc1 and Sdc4 are indicated at the respective amino acid number and sheddases according to Manon-Jensen *et al.* (2010) (shown in black). The predicted shedding sites for Sdc2 and Sdc3 include only the prediction for MMP2, MMP3 and MMP14 and thrombin. The shedding sites for Sdc2 and Sdc3 are generated using a cleavage site prediction tool (shownin grey). Again, the amino acid is indicated with the predicted sheddase. HS-GAG chains are shown in blue colour and chondroitin sulfate GAG chains are shown in orange.

Table 1

List of soluble syndecans as biomarkers for various diseases including the respective reference

Sdc1			
Disease	**Sample**	**Regulation**	**References**
Sepsis	Arterial plasma, serum	Significantly elevated levels, correlation with cardiovascular Sequential Organ Failure Assessment score	Nelson et al. (2008); Steppan et al. (2011)
Sepsis survival after major abdominal surgery	Plasma	Patients with post-operative sepsis showed increased levels; levels associated with survival after sepsis	Holzmann et al. (2018)
Acute traumatic endotheliopathy in isolated severe brain injury	Plasma	Sdc1 levels above 30.5 ng·mL^{-1} indicate patients with traumatic brain injury-associated coagulopathy	Albert et al. (2018)
Trauma patients	Serum/plasma	High levels of Sdc1 are associated with inflammation, coagulopathy and increased mortality, a syndecan-1 level ≥ 40 ng·mL^{-1} identified patients with worse outcome	Johansson et al. (2011); Johansson et al. (2012); Gonzalez Rodriguez et al. (2017)
Microvascular glycocalyx degradation	Plasma	Syndecan-1 correlates with glycocalyx thickness and permeability changes	Torres Filho et al. (2016)
KD	Serum	Sdc1 levels may indicate endothelial damage and inflammation KD	Luo et al. (2018a)
Pulmonary embolism	Blood	Increased levels of Sdc1 in high risk pulmonary embolism patients	Lehnert et al. (2017)
Multicentric Castleman's disease	Bronchoalveolar lavage fluid	Marked elevation of soluble Sdc1	Hasegawa et al. (2007)
Heart failure	Plasma	Syndecan-1 correlates with fibrosis biomarkers	Tromp et al. (2014)
Ventricular remodelling after myocardial infarction	Serum	Increased levels of soluble Sdc1	Lei et al. (2012)
Takotsubo cardiomyopathy	Blood	Sdc1 is significantly increased in the acute stage of TCC	Nguyen et al. (2017)
AKI	Blood	Prognostic marker to assess the risk of AKI	Liborio et al. (2015); Neves et al. (2015); de Melo Bezerra Cavalcante et al. (2016)
Chronic kidney disease	Plasma	Plasma levels were increased compared to the healthy control group	Padberg et al. (2014)
Ischaemia–reperfusion injury	Arterial blood	Elevated levels of Sdc1	Rehm et al. (2007)
DIC	Serum/plasma	Correlates with increased levels of Sdc1, predicts DIC in patients with sepsis	Ikeda et al. (2018)
Hypocoagulation	Serum/plasma	Increased levels are associated with hypocoagulation in patients with sepsis	Ostrowski et al. (2015)
GVHD	Serum	Sdc1 levels elevated in patients who developed acute GVHD after allogeneic stem cell transplantation	Seidel et al. (2003)
Crohn's disease	Serum	Higher Sdc1 levels compared to normal population	Zhang et al. (2013); Cekic et al. (2015)
Small bowel damage in children with CD	Serum	Elevated levels of Sdc1 in children with CD, correlation of Sdc1 levels and mucosal damage	Yablecovitch et al. (2017)
SLE	Serum	Higher levels in SLE patients with nephritis compared to RA patients and healthy control group, possible marker for active SLE	Minowa et al. (2011); Kim et al. (2015); Mosaad et al. (2017)
Liver fibrosis stage in patients with hepatitis C	Serum	Suggested as non-invasive marker to predict liver fibrosis stage	Zvibel et al. (2009)
Hantavirus infection	Plasma	Sdc1 was associated with disease severity (as wells as levels of thrombocytes, albumin, IGFBP-1, decreased blood pressure)	Connolly-Andersen et al. (2014)
Type I diabetes mellitus	Serum	Sdc1 is upregulated	Svennevig et al. (2006)

continues

Table 1

(Continued)

Sdc1			
Disease	**Sample**	**Regulation**	**References**
PE	Serum/plasma	Statistical differences in serum between PE and normal pregnancy, Sdc1 in plasma is significantly lower before the onset of PE	Gandley *et al.* (2016); Alici Davutoglu *et al.* (2018)
HELLP syndrome	Serum	Sdc1 levels increase in normal pregnancy but even higher in women with HELLP	Hofmann-Kiefer *et al.* (2013)
Rhegmatogenous retinal detachment	Subretinal fluid/ vitreous fluid	Significant increase of Sdc1	Wang *et al.* (2008)
Systemic sclerosis	Serum	Significantly higher than in healthy control group	Wu *et al.* (2016)
Pleural malignancies	Pleural effusions	Sdc1 levels can distinguish malignant and benign disease	Mundt *et al.* (2014)
Lung cancer	Serum	High Sdc1 levels were associated with a poor survival rate	Joensuu *et al.* (2002); Anttonen *et al.* (2003)
Myeloma (multiple)	Serum	Possible prognostic marker	Dhodapkar *et al.* (1998); Seidel *et al.* (2000); Yang *et al.* (2002); Aref *et al.* (2003); Janosi *et al.* (2004); Lovell *et al.* (2005); Maisnar *et al.* (2006); Scudla *et al.* (2009); Kim *et al.* (2010)
Hepatocellular carcinoma	Serum	High levels in patients with hepatocellular carcinoma detected, high levels associated with greater risk of tumour recurrence and death	Metwaly *et al.* (2012); Nault *et al.* (2013)
(Metastatic) CRC	Serum	Baseline Sdc1 is suggested as prognostic marker for overall survival in metastatic CRC, Sdc1, among others, may be involved in tumour progression and can be used for prognosis of CRC patients	Jary *et al.* (2016); Mitselou *et al.* (2016)
PC	Serum	Significant higher Sdc1 levels in advanced cases of PC, independent factor of adverse overall and disease-specific survival	Szarvas *et al.* (2016)
Hodgkin's lymphoma	Serum	Serum levels are elevated but do not strongly correlate with other parameters, further evaluation is required	Vassilakopoulos *et al.* (2005)
Lymphocytic leukaemia	Plasma	Soluble Sdc1 in combination with beat2-M and Rai stage may replace testing for IgVH mutation status	Jilani *et al.* (2009)
Breast cancer	Serum	Positive correlation between soluble Sdc1 and tumour size	Malek-Hosseini *et al.* (2017)
Bladder cancer	Serum	Increased levels in sera of bladder cancer patients	Sanaee *et al.* (2015)
Sdc2			
Disease	**Sample**	**Regulation**	**References**
Colon cancer	Serum	Sdc2 detectable in majority of colon cancer patients, while all healthy patients were negative	Choi *et al.* (2015)
Keloid tissue	Tissue	Up-regulated in keloid tissue	Mukhopadhyay *et al.* (2010)
Sdc3			
Soluble Sdc3 has not been reported to be a suitable biomarker.			
Sdc4			
Disease	**Sample**	**Regulation**	**References**
Acute bacterial pneumonia	Serum	Up-regulation (at the onset, mild pneumonia compared to severe pneumonia)	Nikaido *et al.* (2015)

continues

Table 1

(Continued)

Sdc4			
Disease	**Sample**	**Regulation**	**References**
IIP	Serum	Down-regulation in acute exacerbation, patients with higher baseline have worse prognosis for IIP (prognostic predictor)	Sato *et al.* (2017)
Severe community acquired pneumonia	Serum	Patients with Sdc4 levels below 6.68 ng·mL^{-1} have a higher mortality (prognostic predictor)	Luo *et al.* (2018b)
Heart failure in patients with hypertension	Serum	Sdc4 levels above 2.3 ng·mL^{-1} (among others) are significant predictor for heart failure	Bielecka-Dabrowa *et al.* (2015)
Adverse LV remodelling in patients with dilated cardiomyopathy	Serum	Sdc4 correlated positively with LV diastolic/systolic diameters, might be useful in predicting LV remodelling	Takahashi *et al.* (2011); Bielecka-Dabrowa *et al.* (2013)
Atopic dermatitis	Serum	Levels upregulated compared to control group and correlate with disease severity, eczema area, severity index and itch visual analogue scale scores	Nakao *et al.* (2016)
Cardiovascular mortality in HD patients	Serum	Sdc4 levels are increased in HD patients, levels correlate with echocardiographic parameters (predictor for cardiovascular mortality)	Jaroszynski *et al.* (2016)

AKI, acute kidney injury; CD, celiac disease; CRC, colorectal cancer; DIC, disseminated intravascular coagulation; KD, Kawasaki disease; GVHD, Graft-versus-host disease; HELLP, Haemolysis, elevated liver enzymes and low platelets; HD, haemodialysis; IIP, idiopathic intestinal pneumonia; PC, prostate cancer; PE, preeclampsia; RA, rheumatoid arthritis; SLE, Systemic lupus erythematosus; TCC, terminal complement complex.

inflammatory response to toxins, chemicals, allergens and pathogens is dysregulated in the absence of Sdc1 or when its shedding is inhibited (Kainulainen *et al.*, 1998; Kato *et al.*, 1998), suggesting that Sdc1 shedding is activated to ensure adequate tissue response to inflammation. Consequently, Sdc1 has been proposed to be a biomarker for sepsis survival after major abdominal surgery, as well as for acute traumatic endotheliopathy in isolated severe brain injury, and for small bowel mucosal damage in children with celiac disease (Yablecovitch *et al.*, 2017; Albert *et al.*, 2018; Holzmann *et al.*, 2018).

The activation of Sdc2 shedding has been described for cancer cells. In particular, the MMP7-induced shedding of Sdc2 was detected in colon cancer cells *in vitro* (Choi *et al.*, 2011). Patients with advanced colon cancer exhibited significantly higher Sdc2 serum levels compared to a healthy control group, which was mainly negative for Sdc2 serum levels (Choi *et al.*, 2015). Furthermore, Sdc2 and FGF-2 were overexpressed in keloid tissue. The authors suggested that both proteins interact with each other, resulting in shedding of Sdc2 and that shed Sdc2 might be involved in the keloidic phenotype (Mukhopadhyay *et al.*, 2010).

Besides its role in cancer, shed Sdc2 has been linked to angiogenesis, as its expression is increased during endothelial cell angiogenic processes (Fears *et al.*, 2006). Shed Sdc2 regulated angiogenesis by inhibiting endothelial cell migration in human and rodent models and thereby reduced tumour growth (De Rossi *et al.*, 2014).

Soluble Sdc4 in serum is mainly associated with pneumonia and heart failure. In patients with mild pneumonia, Sdc4 was increased in comparison to patients with severe pneumonia. Interestingly, a short-term antibiotic therapy further increased Sdc4 levels, leading the authors to the suggestion that Sdc4 might have an anti-inflammatory function (Nikaido *et al.*, 2015). The same research group

showed that Sdc4 levels were increased in patients with idiopathic interstitial pneumonia. Again, the authors propose that baseline serum Sdc4 levels were indicative for the prognosis, showing that higher serum levels of Sdc4 were associated with a worse prognosis than lower baseline levels (Sato *et al.*, 2017). Sdc4 serum levels were also associated with severe community-acquired pneumonia, and these increased serum levels were linked to a higher mortality rate (Luo *et al.*, 2018b).

Furthermore, high serum Sdc4 levels were found to be a significant predictor of heart failure in patients with hypertension (Bielecka-Dabrowa *et al.*, 2015), and Sdc4 was also proposed as a suitable biomarker for the adverse left ventricular (LV) remodelling in patients with dilated cardiomyopathy (Bielecka-Dabrowa *et al.*, 2013). This finding was corroborated in another study in which serum Sdc4 levels were proposed to be a biomarker for LV remodelling in heart failure (Takahashi *et al.*, 2011). Serum Sdc4 levels were also increased in haemodialysis patients and correlated with geometrical echocardiographic parameters. This study suggested Sdc4 as a predictor for cardiovascular mortality in haemodialysis patients (Jaroszynski *et al.*, 2016). Apart from cardiovascular diseases and pneumonia, increased Sdc4 serum levels have also been reported in patients with atopic dermatitis. In this study, Sdc4 levels correlated with the disease severity as well as eczema area, the severity index and visual analogue scale scores for itch (Nakao *et al.*, 2016).

In particular, serum levels of soluble Sdc1 and Sdc4 have been shown to be associated with various diseases. Therefore, it will be a challenge to differentiate the cause of elevated syndecan levels in different patients to decide to which disease they might relate. More distinct analyses of the shedding site and/or modification of the HS-GAG chains will improve the sensitivity of the suggested biomarker for the respective disease.

Current therapies targeting syndecans

Because of the involvement of syndecans in various diseases as already discussed, many agents interfering with the expression and function of syndecans are currently under investigation to improve the clinical management of several diseases. In particular, the role of heparan sulfate proteoglycans (HSPGs) and heparanases in several malignant tumours is currently the focus for novel therapeutic approaches. Heparanase-1 has been associated with increased metastasis and poor prognosis; therefore, silencing of this heparanase has been performed and found to be successful in reducing the invasiveness and migratory capabilities of human osteosarcoma cells (Fan *et al.*, 2011). Further evidence for the therapeutic potential of heparanase usage comes from the study of Wang *et al.* (2013); showing that low MW heparin ameliorated experimental colitis in mice by down-regulating IL-1β and inhibiting Sdc1 shedding in the intestinal mucosa. These studies highlight the important role of the HS chains and also the therapeutic potential in modifying or cleaving the side chains to modulate syndecan functions.

Furthermore, antibodies or short peptide inhibitors for Sdc1 have been tested for their efficacy in cancer therapy. One example is synstatin, which is a selective inhibitor of αvβ3 or αvβ5 integrin and insulin-like growth factor 1 receptor interaction and thus preventing tumour survival (Rapraeger *et al.*, 2013; Beauvais *et al.*, 2016). Synstatin is a recombinant Sdc1 protein, which has been truncated to the shortest sequence that retained the full inhibitory activity (SSTN92-119). Furthermore, a soluble Sdc1- Fc hybrid molecule was generated by fusing the ectodomain of Sdc1 to the Fc domain of a human IgG. The authors describe that the sdc1-Fc hybrid molecule acted on various levels to prevent HIV-infection, as well as herpes simplex virus infection. The HS chains of the syndecan-Fc hybrid molecule were essential for the HIV-1 neutralization (Bobardt *et al.*, 2010). The soluble form of the Sdc1 has also been shown to act as a tumour suppressor molecule by inhibiting tumour growth and inducing apoptosis of some cancer cell lines *in vitro*. Therefore, analogues of Sdc1 were produced by carbodiimide conjugation of GAG chains to a protein scaffold, generating synthetic proteoglycans. These synthetic proteogylcans were shown to

Figure 4

Overview of the various therapeutic strategies using soluble syndecans or targeting syndecan signalling for different diseases. (A) Inhibition of HS cleavage; (B) heparin treatment; (C) blocking antibody; (D) soluble Sdc and/or analogues.

inhibit myeloma cell viability *in vitro* and *in vivo* in a mouse model of breast cancer (Pumphrey *et al.*, 2002). Not only soluble Sdc1 has been shown to exhibit therapeutic potential, there is also evidence for a beneficial effect of shed Sdc2. Shed Sdc2 inhibits angiogenesis by inhibiting endothelial cell migration and thereby reduces tumour growth (De Rossi *et al.*, 2014). This finding gives rise to a novel therapeutic strategy to target pathologies that are characterized by new blood vessel formation, like different cancers, infectious diseases and autoimmune disorders.

These studies highlight the anticancer and antiviral activities of GAG chain-containing proteins and provide the foundation for future development of synthetic proteoglycans as novel therapeutic agents.

Interestingly, also the overexpression of the C-terminal fragment of Sdc1 has been shown to suppress migration and invasion of tumour cells. This inhibitory effect, however, was only seen in cells expressing endogenous Sdc1 but not in Sdc1 knockout cells. The C-terminal Sdc1 fragment suppressed tumour cell migration and increased basal phosphorylation of Src and FAK. The authors explain the observed effects with an antagonizing mechanism of the C-terminal fragment for the Sdc1-dependent tumour cell migration *in vitro* and *in vivo* by dysregulating pro-adhesive signalling pathways (Pasqualon *et al.*, 2015).

There is also evidence that the blockade of Sdc4 using a blocking antibody might have a positive effect in preventing cartilage destruction in a mouse model of osteoarthritis (Echtermeyer *et al.*, 2009). The authors describe that Sdc4-mediated cartilage destruction in osteoarthritis is mediated by binding of the aggrecanase (ADAMTS-5) to the side chains of Sdc4, thereby fixing ADAMTS-5 at the cell surface. The activation of ADAMTS-5 is mediated by MMP3 expression, which is regulated in an IL-1-dependent manner by Sdc4, as Sdc4 regulates the sensitivity of chondrocytes to IL-1 signalling (Echtermeyer *et al.*, 2009).

Figure 4 summarizes the current therapeutic strategies involving modification of Sdc-dependent signalling pathways. Four different approaches can be differentiated. The first approach is based on the inhibition of HS side chain cleavage and thereby inhibits the HS-fragment-induced activation of inflammatory signalling cascades and Sdc-shedding (Figure 4A). The second strategy is based on the anti-inflammatory effect of low MW heparin, although the exact mechanism of the ant-inflammatory effect is not known (Figure 4B). The third mechanism is based on the blockade of Sdc4 signalling and inhibition of IL-1-dependent inflammatory signals. Again, the exact mechanism of this blockade is not described (Figure 4C). The last approach is based on the use of soluble syndecans or their synthetic variants. There are several studies using either full length soluble syndecans or truncated forms or even synthetic variants with synthetic HS side chains attached (Figure 4D).

Conclusion

The current knowledge about syndecan shedding highlights the role of soluble syndecans in various diseases. However, the main function of soluble syndecans depends mainly on the presence of GAG chains, which are known to be modified during ageing, disease and cell differentiation (Bassett *et al.*, 2006). At the same time, the respective sheddases are modulated depending on external stimuli, cell differentiation and inflammation. The current knowledge just elucidates parts of the highly complex temporal and spatial regulation of syndecan expression, regulation of morphogen binding and further shedding during ageing and diseases. This makes the usage of soluble syndecans as biomarkers difficult, especially as more than one stimulus might evoke shedding of the same syndecan, thereby reducing the specificity of the potential biomarker. There is clearly a therapeutic potential for soluble syndecans in different diseases; however, more insight in the role GAG chains and GAG chain modification is needed to fully understand the different roles and effects. Syndecan core proteins most likely serve mainly as the anchorage for these highly complex sugar chains, building the basis for disease regulated shedding.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017a,b).

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Conflict of interest

The authors declare no conflicts of interest.

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